REMARKS

Claim Amendments

In an effort to expedite the prosecution of this application to allowance, the above amendments have been made to focus the claims on the preferred embodiment of treating a solid tumour in a warm-blooded animal by the administration of ZD6474 in combination with 5-FU, as follows:

- "Use" **claim 1-7** have been cancelled as being in a Swiss-type format, which is generally not acceptable under US practice.
- Pharmaceutical composition and kit **claims 8-13** have been cancelled to focus the prosecution of this application on the method of treatment aspect of the present invention.
- Method of treatment **claim 14** has been amended to insert the chemical name and structure of ZD6474, and to more specifically direct the claims to the treatment of a solid tumour cancer in a warm blooded animal by the administration of ZD6474 in combination with 5-FU. The reference to "such as a human" has been deleted as generally not being acceptable under US practice. Support for the treatment of a cancer involving a solid tumour is found, *inter alia*, at page 5, lines 3-7 and at page 17, lines 8-18.
- New dependent method of treatment **claim 15** is directed toward the method of claim 14 wherein the the solid tumour cancer is selected from a tumour of the colon, breast, prostate, lungs and skin. Support for claim 15 is specifically found, *inter alia*, at specification page 17, lines 8-10.
- New dependent method of treatment **claim 16** is directed toward the method of claim 14 wherein the solid tumour cancer is a tumour of colorectal cancer. Support for claim 16 is specifically found, *inter alia*, at specification page 17, lines 16-18 and comparative tests reported at specification pages 33-36.
- New dependent method of treatment **claim 17** is directed toward the method of claim 14 additionally comprising the administration of ionising radiation. Support for claim 17 is

found throughout the specification, *inter alia* at page 11, lines 25-29 and page 12, line 9; and at page 13, lines 20-26.

The above amendments are being made without abandonment or waiver of Applicants' right to prosecute any and all subject matter deleted thereby in one or more continuing applications.

It should be clear that no new matter has been added by the above amendments, and entry thereof is believed to be in order and is respectfully requested. Following entry of these amendments, claims 14-17 are pending in this application.

Claim Rejections - 35 USC § 112 and 35 USC § 101

The rejections of claim 1-7 under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 101 have been obviated by the cancellation of these claims.

Claim Rejections - 35 USC § 103

Claims 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin *et al.* This ground for rejection is respectfully traversed, particularly in view of the above amendments to the claims.

Original claims 8-14 that were examined in this Action were drawn to a pharmaceutical composition and kit comprising ZD6474 and 5-FU and/or CPT-11 (claims 8-13, now cancelled) and a method of treating cancer, comprising administering ZD6474 and 5-FU and/or CPT-11, optionally with an effective amount of ionising radiation (claim 14). The claims as presently amended are all method of treatment claims directed toward the treatment of a solid tumour cancer comprising administering a combination of ZD6474 and 5-FU, optionally with an effective amount of ionising radiation.

In formulating the rejection of claims 8-14, the Examiner notes that Hennequin *et al.* discloses a method for the treatment of cancer in a warm-blooded animal (citing page 1, lines 1-6 and page 28, lines 11-17), which comprises administering a compound of formula I as generally described beginning on page 3 of the reference, and that ZD6474 is specifically identified as a compound of Formula I (citing claim 8). The Examiner then asserts that Hennequin *et al.* further

teaches combining ZD6474 with additional antineoplastic drugs including 5-FU and CPT-11 (irinotecan) and combinations thereof, and that combination therapy is normal practice in the field of medical oncology (citing page 26, lines 22-27 and page 27, lines 20-30). The Examiner concludes that therefore, "it would have been obvious to one of ordinary skill in the art at the time of the invention to administer ZD6474 with 5-FU and/or CPT-11, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success."[1]

At page 3 of the present disclosure Applicants specifically acknowledge the disclosure on page 26 of Hennequin *et al.* (WO 01/32651), now cited by the Examiner, noting that:

> In WO 01/32651 it is stated that compounds of that invention: "may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment."

The present specification at page 3 continues, noting that WO 01/32651 describes examples of such conjoint treatment including surgery, radiotherapy and many types of chemotherapeutic agent including 5-fluorouracil (5-FU) and irinotecan (CPT-11). In fact WO 01/32651 expands upon the conjoint chemotherapy treatment, describing at page 27 five main categories of therapeutic agent as follows:

> (i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate));
>
> (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide, abarelix), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example

[1] The Examiner cites *In re Kerkhoven* at page 4 of the Action as a further ground for the obviousness rejection of the pharmaceutical composition and kit claims, which need not be further addressed at this time in that this ground has been obviated by the cancellation of pharmaceutical composition claims 8-10 and kit claims 11-13.

metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

(WO 01/32651, page 27, lines 1-30).

The compound that is ZD6474 is just one of a number of compounds that are within the scope of the WO 01/32651 disclosure or described therein, and 5-fluorouracil (5-FU) and irinotecan (CPT-11) are just two of the many antiproliferative/antineoplastic drugs mentioned in the above-quoted subparagraph (v), which is only one of the five different categories of chemotherapeutic agent listed on page 27 of WO 01/32651 that can be used in the conjoint treatments. It is therefore respectfully submitted that in the absence of hindsight from the present invention, there is no suggestion or motivation for the skilled person to select the particular combination of ZD6474 and 5-FU out of the myriad of possible combinations disclosed in Hennequin *et al.*, and therefore that *prima facie* obviousness has not been established.

Nevertheless, even if *prima facie* obviousness had been established, it is overcome by the comparative evidence presented at pages 33-36 of the present specification, with particular reference to the presently claimed combination of ZD6474 and 5-FU.

Nowhere in WO 01/32651 does it state that use of a compound of formula (I) with other treatments will produce surprisingly beneficial effects. However, Applicants state at page 3, lines 20 *et seq.* of the present application that "[u]nexpectedly and surprisingly we have now found that the particular compound ZD6474 used in combination with a particular selection of combination therapies, namely with one of: 5-FU; CPT-11; and 5-FU and CPT-11," produces significantly better effects on solid tumours, and significantly better effects in colorectal cancer than any one of ZD6474; 5-FU; CPT-11; and 5-FU and CPT-11 used alone.

This surprising beneficial result with respect to the *presently claimed* combination of ZD6474 and 5-FU is demonstrated by the comparative data presented at pages 33-36 of the specification. The Examiner's attention is drawn in particular to the comparative tumour growth inhibition and tumour regression data presented on the table at pages 35-36 and the comparative mean tumour volume data graphically shown on page 35.

This data compares the relative inhibition of tumour growth over 13 days in four randomized groups of 13-15 *Nude* mice undergoing the treatment regimens set out on the table at pages 34-35:

- Group 1 being the control, treated with the vehicles only for ZD6474 and 5-FU;
- Group 2 being treated with ZD6474 and with the vehicle only for 5-FU;
- Group 3 being treated with the vehicle only for ZD6474 and with 5-FU; and
- Group 4 being treated with ZD6474 and with 5-FU.

The resulting data are tabulated in the table spanning pages 35 and 36, showing, in the second column, growth inhibition over the period of treatment by comparison of the differences in tumour volume between control and treated groups and, in the fourth column, the number of tumours in each group which had *regressed* by $\geq$10% over the period of treatment when compared with their pre-treatment volume. The graph at page 35 illustrates the "mean tumour volume" of the four Groups relative to one another over the 13 day treatment period, with the bottom line representing the Group 4 data for treatment with the claimed combination of ZD6474 and 5-FU.

As summarized at page 36 of the specification, lines 4-9:

- The combination of 5-FU with ZD6474 produced a *significantly greater inhibition of tumour growth than 5-FU* alone (P= 0.018 at day 13, by one-tailed two-sample t test).
- The combination of 5-FU with ZD6474 produced a *significantly greater inhibition of tumour growth than ZD6474 alone*, (P= 0.027 at day 13, by one-tailed two-sample t test).
- The combination of 5-FU with ZD6474 produced *more tumour regressions* (62%) than ZD6474 alone (33%) or 5-FU alone (40%).

Thus, it can be seen from this graph and table that there is marked effect on the tumour growth by treatment with the combination compared to treatment with either agent alone. Both ZD6474 and 5-FU decrease the rate of tumour growth with regression in some tumours, but the combination unexpectedly shows regression in a much higher proportion of the animals (8/13), and *overall shows inhibition of tumour growth of 107%*, which means that overall there was *tumour regression* with Group 4, treated with the combination of ZD6474 and 5-FU as presently claimed. This *tumour regression* is graphically shown by the negative slope of the bottom (Group 4) line representing "Mean Tumour Volume" to day 13 compared with the positive slope for the other test regimens.

Therefore any *prima facie* obviousness that might be said to arise from the Hennequin *et al.* disclosure has been overcome by the demonstrated unexpected significant beneficial effect on tumour growth inhibition and overall tumour regression by the combination treatment with ZD6474 and 5-FU as presently claimed. Withdrawal of this obviousness ground for rejection is therefore respectfully requested.

Conclusion

All grounds for rejection having been addressed and, it is believed, overcome by the above amendments and/or remarks, the claims should now be in condition for allowance and a notice to that effect is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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